60 ml of EtOH was refluxed for 8 hr. The reaction mixture was concentrated *in vacuo*, made alkaline with 40% NaOH, and extracted ($CHCl_3$). The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was recrystallized three times.

Other members of this series (I, A = $COCH_2$) were prepared following the above procedure. The resulting products were either crystallized from the appropriate solvents, when solid, or, when oily, converted to the maleate or dihydrochloride salts by addition of acetone solution of the base to the ethanolic maleic acid or to the excess 5 *N* 2-propanolic–HCl.

N^1-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-N^4-(*o*-tolyl)piperazine Monohydrochloride (39).—To a solution of 5.0 g (0.02 mole) of N-(*o*-tolyl)piperazine dihydrochloride in 100 ml of EtOH, 3 ml (~0.03 mole) of aqueous formaldehyde (37–41%), and 5.0 g (0.024 mole) of 3,4,5-trimethoxyacetophenone was added and the mixture was refluxed for 7 hr. Additional aqueous formaldehyde (3 ml) was added and reflux continued further for 7 hr. The reaction mixture was concentrated to half of its volume and allowed to cool, when a white shining crystalline compound separated out. This was collected by filtration, dried, and recrystallized.

The hydrochloride was converted quantitatively to the free base which was recrystallized from EtOH. The maleate salt of this base was prepared by the addition of its solution in ether to the calculated amount of maleic acid in EtOH.

The rest of the ketonic Mannich bases (I, A = $COCH_2CH_2$) were prepared by following the method described above.

β,β-Bis[N^4-(*m*-tolyl)-N^1-piperazinyl]-3,4,5-trimethoxypropiophenone.—To a solution of 3.73 g (0.015 mole) of 1-(*m*-tolyl)-piperazine dihydrochloride in 70 ml of EtOH, 1.5 ml (~0.015 mole) of aqueous formaldehyde, and 3.45 g (0.0165 mole) of 3,4,5-trimethoxyacetophenone were added and the mixture was refluxed for 7 hr. Aqueous formaldehyde (1.5 ml) was again added and reflux continued for another 7 hr. The reaction mixture was concentrated to one-third of its volume and added to 200 ml of dry acetone; the resulting solid on filtration was hygroscopic. It was dissolved in water, and the free base was liberated with 10% aqueous NaOH and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue, on keeping for 2 days over anhydrous $CaCl_2$ in a vacuum desiccator, turned into a fine yellow solid, mp 89° dec (softens at 70°). *Anal.* ($C_{35}H_{46}N_4O_4$) C, H, N.

N^1-[γ-Hydroxy-γ-(3,4,5-trimethoxyphenyl)propyl]-N^1-(*o*-tolyl)-piperazine Dihydrochloride (40).—A suspension of 6.52 g (0.015 mole) of **39** in 250 ml of MeOH was adjusted to pH 10 with 50% aqueous NaOH and cooled in an ice bath. While stirring at 0°, 0.9 g of $NaBH_4$ was added over a period of 15 min. The reaction mixture was stirred for 3 hr at room temperature. It was then cooled to 5° and acidified to pH 2 with concentrated HCl. After stirring for 15 min the pH was again adjusted to 10, with 50% aqueous NaOH. The reaction mixture was evaporated to half of its volume, diluted with 250 ml of H_2O, and extracted ($CHCl_3$). The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oily residue was taken up in 60 ml of Me_2CO and added to 30 ml of 5 *N* 2-propanolic–HCl. The white granular solid thus obtained was recrystallized.

N^1-[γ-(3,4,5-Trimethoxybenzoyl)propyl]-N^4-(*o*-methoxyphenyl)piperazine Dihydrochloride (49).—γ-Chloro-3,4,5-trimethoxybutyrophenone (2.73 g, 0.01 mole) and 3.84 (0.02 mole) of N-(*o*-methoxyphenyl)piperazine were mixed and warmed. The mixture was kept for 6 hr at room temperature and then heated at 100° for 4 hr. After cooling, water was added, and the reaction mixture was extracted twice with 40 ml of $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was recrystallized to give base which was also converted to its dihydrochloride salt.

Other members of this series (I, A = $COCH_2CH_2CH_2$) were prepared following the above procedure. The resulting products were either recrystallized, when solid, from the appropriate solvents, or converted, when oily, to the dihydrochloride salts.

N^1-[δ-Hydroxy-δ-(3,4,5-trimethoxyphenyl)butyl]-N^4-(*o*-methoxyphenyl)piperazine dihydrochloride (50) was obtained from **49** by reduction with $NaBH_4$, following the procedure described for **40**.

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Transformations in the Morphine Series. II.[1a] A New Position Isomer of Dihydromorphinone[1b]

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The transformation of dihydrocodeinone (I) to a new position isomer (VII) of dihydromorphinone is described. In mice, VII elicited roughly one-third the analgetic activity of codeine. These data further demonstrate how critical are the relative points of linkage of the ethanamine system in respect to analgetic activity.

The numerous attempts at structural modification of morphine and its congeners with the view to enhancing pharmacological utility while concomitantly depressing less desirable side effects have been fully documented.[3] Recently[1a] we reported a novel transformation of codeine to an analog of the potent synthetic analgetic phenazocine in which a 14-fold increase in analgetic power over codeine was achieved. The present communication deals with another approach in this area.

Well known is the fact that in the morphine group of alkaloids the nitrogen end of the ethanamine system is linked to C-9 while the carbon terminus (normally at C-13) may, in certain instances, be rearranged to another position, *e.g.*, C-14 in metathebainone.[4] It occurred to us that useful chemical as well as pharmacological information would accrue if it were possible to shift the nitrogen end of the basic chain to a position other than C-9 without disturbing the remaining salient features of the molecule. To this end, dihydrocodeinone (I) was selected as the starting material for the envisaged transformation. Utilizing standard procedures, I-methiodide was degraded (Hofmann) to the corresponding methine and the latter was reduced to the dihydro derivative (II). Treatment of a warm,

(1) (a) Paper I: L. J. Sargent and J. H. Ager, *J. Med. Chem.*, **6**, 569 (1963); (b) 1,2,3,4,11,12-hexahydro-7-hydroxy-3-methyl-4,12-methano-10H-naph[6bo][1′,8′:3,4,5]furo[2,3-*d*]azepin-5(5aH)-one.

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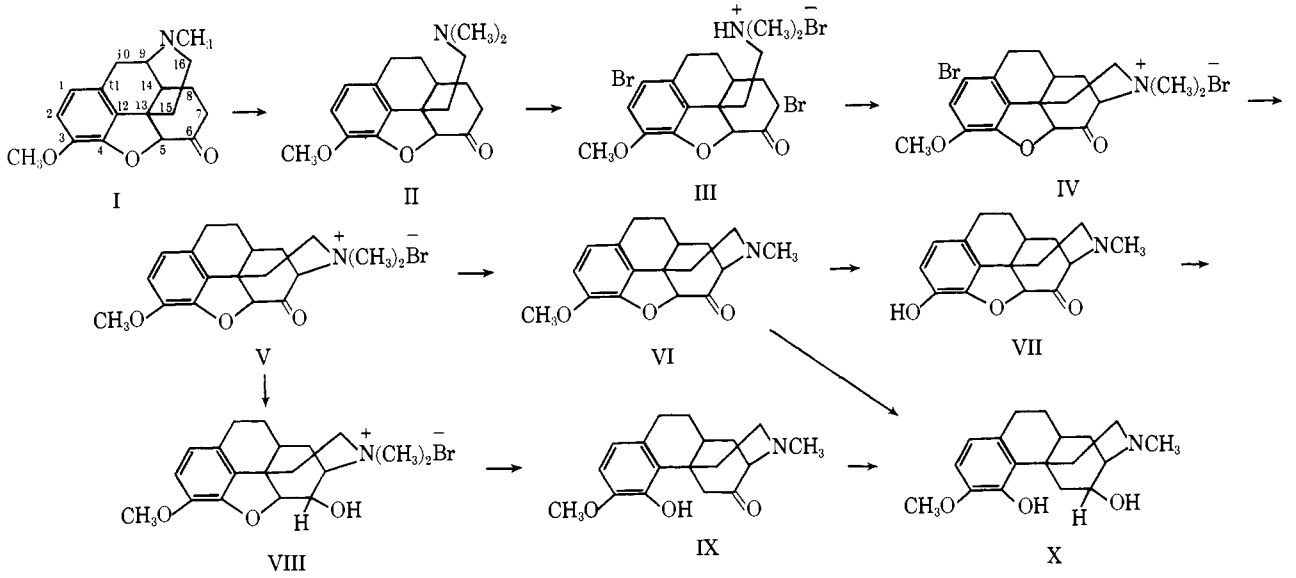
(3) See, for example, (a) Collected Papers—Report of Committee on Drug Addiction 1929–1941, National Research Council, Washington, D. C., 1941; (b) N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. World Health Organ.*, **17**, 569 (1957), and previous papers in this series.

(4) C. Schöpf and F. Borkowsky, *Ann.*, **458**, 148 (1927).

SCHEME I



glacial acetic acid solution of the latter with 2 moles of bromine led to dibromodihydrocodeinone methine hydrobromide (III) in good yield (see Scheme I).

Drawing on previous experience in this general area[5] one of the two bromine atoms was assigned to C-1, while positions 5 and 7 (both α to the carbonyl function at C-6) were considered likely sites for the second halogen atom. In view of the latter alternatives it was necessary to establish which of the two positions was, in fact, involved before proceeding further. Useful nmr studies on a number of morphine alkaloids and derivatives have been carried out recently by several investigators.[6] Among other observations was the significant finding that the proton at C-5 gave rise to a distinct peak (or peaks) which, depending on the nature of the compound, occurred between 4.35 and 5.25 ppm. Moreover, the aromatic protons at C-1 and C-2 were easily identified between 6.54 and 6.72 ppm. Table I shows the observed chemical shifts (ppm) ascribed to the 5β-hydrogen atom in the various compounds examined in this investigation (see ref 5a and 7).

It will be noted that the 5β-proton in VI appears as a split peak approximately 10 cps (downfield) from the usual zone reported for this proton in a series of morphine derivatives.[6] This may, conceivably, be attributed to a change in environment of the ethanamine system from its normal point of attachment (C-9) to C-7. The split peak, moreover, may be accounted for by coupling of the 5-proton with the proximate proton(s) at C-15 (on the ethanamine chain).

Since these data effectively rule out C-5 in favor of C-7 as the location of the alicyclic bromine atom, it was of further interest to determine whether the halogen was axially or equatorially oriented. Referring to cyclohexanone and 2-(e)-bromocyclohexanone (with respective infrared carbonyl absorption bands at 1712 and 1734 cm^{-1}) as models,[8] II and III showed cor-

TABLE I

Compd	δ, ppm	Solvent
II	5.05	$CDCl_3$
III	4.90	SO_2 (liq)
IV	5.04	SO_2 (liq)
V	5.06	SO_2 (liq)
VI	5.36/5.40 (split)	$CDCl_3$
IX	None	$CDCl_3$
X	None	$CDCl_3$
7-Methyldihydrocodeinone[5a,7]	5.24	$CDCl_3$

responding bands at 1713 and 1732 cm^{-1}, respectively, in accord with an equatorial halogen orientation. These data also coincide quite well with Gates' observations in respect to the dibromo derivatives of dihydrocodeinone and of *cis*- and *trans*-dihydrothebainone.[5b] Additional evidence in support of the equatorial bromine conformation at C-7 was obtained from optical rotatory dispersion studies. The spectrum of the parent ketone (II) hydrobromide showed a minor positive (Cotton effect) peak at 252 and a major one at 288 mμ, values which remained essentially unaltered in the spectrum of III.[9] On the basis of the above evidence, dibromodihydrocodeinone methine hydrobromide may be represented as shown in III.

Base-induced intramolecular cyclizations of properly constituted α-haloamino ketones to systems in which the nitrogen is part of a new heterocycle have been reported by several investigators.[10] With the view to forming a position isomer of dihydrocodeinone, III was treated with aqueous NH_4OH as described by Blicke and Krapcho[10b] and modified by Saito and May.[11] It should be noted that, in order to satisfy the geometric conditions prerequisite to cyclization, the equatorially oriented bromine atom at C-7 probably undergoes base-catalyzed epimerization to the *trans* axial conformation. In this connection we were not unmindful of the possible transient formation of a Favorskii cyclopropanone

(5) (a) L. F. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936); (b) M. Gates and M. S. Shepard, *ibid.*, **84**, 4125 (1962).

(6) (a) T. Rull and D. Gagnaire, *Bull. Soc. Chim. France*, 2189 (1963); (b) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 104 (1964); (c) T. J. Batterham, K. H., Bell, and U. Weiss, *Australian J. Chem.*, **18**, 1799 (1965).

(7) G. Stork and L. Bauer, *J. Am. Chem. Soc.*, **75**, 4373 (1953).

(8) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963, p 389.

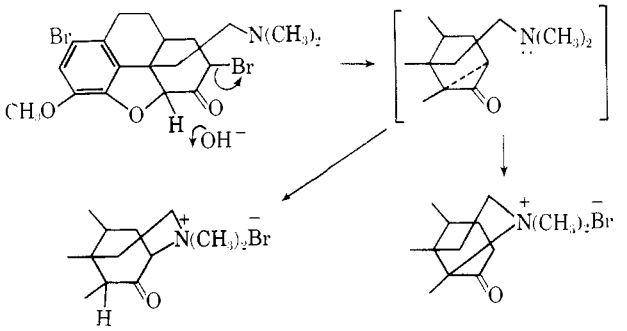
(9) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co. Inc., New York, N. Y., 1960, p 120.

(10) (a) J. A. Barltrop, *J. Chem. Soc.*, 399 (1947); (b) F. F. Blicke and J. Krapcho, *J. Am. Chem. Soc.*, **74**, 4001 (1952); (c) E. L. May and J. G. Murphy, *J. Org. Chem.*, **19**, 618 (1954).

(11) S. Saito and E. L. May, *ibid.*, **26**, 4536 (1961).

intermediate as suggested, in a related case, by Gates in his elegant study of the closure of the 4,5-oxide bridge in the morphine series.[5] Attack by the nitrogen electron pair at either of the two vulnerable positions (*i.e.*, C-5 or C-7) could, conceivably, lead to the formation of two isomers as shown in Scheme II.

SCHEME II

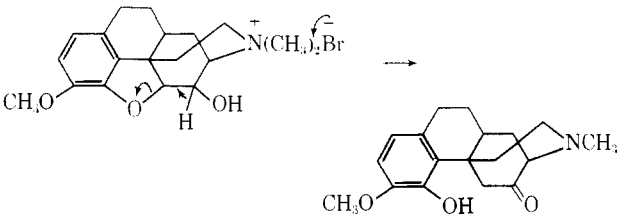


That ring closure had in fact occurred at C-7 was demonstrated by the retention of the 5-proton in IV as exemplified by the nmr peak at 5.04 ppm. Removal of the nonionic halogen (at C-1) in IV was achieved by hydrogenolysis in the presence of palladium on carbon; the resulting methobromide (V) was isomeric with, but different from, dihydrocodeinone methobromide. Pyrolysis of V (in boiling heptanol) yielded the tertiary base VI whose ir and nmr spectra were consonant with the structure shown; moreover, the diazocryptophenol test was *negative*, evidence for the integrity of the 4,5-oxide bridge. The mother liquors resulting from crystallization of VI afforded a small quantity of a crystalline ketocryptophenolic base which proved to be identical in all respects with IXa (*vide infra*).

The Hofmann degradation of the nitrogen-containing ring in dihydrocodeinone has been throughly studied[12] and invariably results in cleavage of the bond joining the nitrogen atom with C-9 owing to the benzylic character of the β-hydrogens at C-10. It was, therefore, not surprising that in the case of the new base VI, lacking benzylic β-hydrogens, the nitrogen ring resisted cleavage under the usual conditions. Conversion of VI to the corresponding phenolic compound (VII) was effected in 80% yield by boiling 48% HBr.

In an attempt to prepare the corresponding 6-carbinol, VI was subjected to hydrogenation (PtO_2) as well as to reaction with $NaBH_4$. Both procedures caused concomitant fission of the 4,5-oxide bridge and led to the same cryptophenol X. Cleavage of the oxide ring as a consequence of diverse reduction procedures is well known.[13] However, opening of this ring under the reducing conditions of $NaBH_4$ appears not to have been observed before. Since models of VI indicate a rather high degree of internal strain, it is very likely that the tendency toward relief of strain leads to ring opening in this instance.

Seeking to circumvent oxide ring cleavage, V was catalytically reduced (PtO_2) and the resulting carbinol methobromide VIII was pyrolyzed in boiling heptanol.



Instead of the expected basic carbinol, a ketocryptophenolic base (of probable structure IX) was isolated.[14] To account for this unanticipated result, one may visualize a concomitant β elimination (presumably to relieve strain) along with the normal expulsion of methyl bromide. It is of interest that $NaBH_4$ reduction of the carbonyl group in IX yielded a substance identical in all respects with X.

In mice (subcutaneous administration), VII showed an ED_{50} of 24.6 mg/kg; this is approximately one-third the activity of codeine.[15]

Experimental Section

Dihydrocodeinone Dihydromethine (II).—Dihydrocodeinone methine[17] (87 g) in 750 ml of 95% EtOH was shaken in H_2 with 9 g of Pd–$CaCO_3$ (5%) until absorption ceased (*ca.* 4 hr). The filtered solution was concentrated (*in vacuo*) and the residual product crystallized from ether; yield 80 g, mp 88–90° (froth). *Anal.* ($C_{19}H_{25}NO_3$) C, H.

The **hydrobromide**, prepared in Et_2O with gaseous HBr, was twice crystallized from MeOH; small prisms, mp 255–257° dec. *Anal.* ($C_{19}H_{26}BrNO_3$) C, H.

1,7-Dibromodihydrocodeinone Dihydromethine Hydrobromide (III).—To a magnetically stirred and heated (55–60°) solution of 29.3 g (0.093 mole) of II in 960 ml of glacial HOAc, a solution of 10.3 ml (0.197 mole) of bromine in 285 ml of the same solvent was added dropwise. The bromine appeared to pile up initially (orange color) and then suddenly react with the evolution of copious quantities of HBr. After all the bromine had been added (*ca.* 6 hr), heating was continued for 15 min, and the system was stirred 30 min longer at 25°. The colorless salt was collected and pressed dry; it was then washed twice by decantation with 400-ml volumes of Et_2O, collected, and air dried; 44 g (86%). A specimen, recrystallized twice from MeOH, had mp 241–243° dec.

Anal. Calcd for $C_{19}H_{24}Br_2NO_3$: C, 41.2; H, 4.37; Br, 43.3. Found: C, 41.8; H, 4.69; Br, 42.2.

The analytical data reflect slight solvolysis of the labile α-halogen atom at C-7. Thus, after two further recrystallizations, the bromine content had fallen to 41.6%.

Cyclization of III to IV.—Concentrated NH_4OH (9 ml) was added to a mixture of 15 g of powdered III, 150 ml of cold H_2O, and 300 ml of Et_2O contained in a 1-l. separatory funnel. The system was shaken vigorously until all but a few particles of III had dissolved. After rapidly transferring the Et_2O layer to a 1-l. round-bottom flask, the aqueous phase was extracted twice again with 50-ml portions of Et_2O. Concentration of the combined Et_2O extracts afforded a syrupy residue which was taken up in 10 ml of warm MeOH, cooled, and diluted portionwise with 500 ml of Me_2CO. The resulting, colorless, crystalline precipitate was kept at 5° (15 hr), filtered, and air dried; 9 g (71%), mp 188–190° dec. A sample was crystallized twice from *i*-PrOH–Et_2O and dried for 6 hr at 105° (*in vacuo*); mp 190–191° dec. *Anal.* ($C_{19}H_{23}Br_2NO_3$) C, H, N.

(12) M. Freund, E. Speyer, and E. Gottmann, *Ber.*, **53**, 2250 (1920).

(13) R. E. Lutz and L. F. Small, *J. Am. Chem. Soc.*, **57**, 2651 (1935). Related procedures that result in opening the cyclic ether bridge in morphine ketone systems are (a) aluminum amalgam in moist ether, H. Wieland and M. Kotake, *Ann.*, **444**, 69, 1925; (b) Na–alcohol, L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939); sodium–liquid ammonia, K. W. Bentley and R. Robinson, *Experientia*, **6**, 353 (1950).

(14) Also formed was a small quantity of an isomeric ketocryptophenolic base (IXa) which will be reported on later.

(15) For details regarding the mouse assay technique, *cf.* E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959), and A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

(16) Elemental analyses and rotations (in 95% EtOH) were carried out by the Analytical Services Section of this laboratory under the supervision of Dr. W. C. Alford. Melting points are corrected. Infrared and nmr spectra were determined in appropriate media as indicated. We are indebted to Dr. E. D. Becker and Dr. F. Weiss of this institute, for helpful discussions regarding the nmr data.

(17) H. Wieland and M. Kotake, *Ann.*, **444**, 69 (1925).

Hydrogenolysis of IV to V.—A solution of IV (9.6 g) in 260 ml of boiling MeOH was digested with Norit, filtered, cooled to room temperature, and shaken in H_2 with 3 g of Pd–charcoal (10% Pd) until gas absorption (1 mole) was complete (*ca.* 18 hr). After decanting the supernate, the catalyst was repeatedly digested with portions of boiling MeOH to remove adsorbed product. Concentration of the combined MeOH solutions at 40° (*in vacuo*) yielded 5.7 g (72%) of colorless, crystalline V. A specimen was crystallized twice from MeOH–Et_2O and had mp 228–230° dec, $[\alpha]^{20}D$ −66.8 ±1.0° (*c* 1.02). *Anal.* ($C_{19}H_{24}BrNO_3$) C, H, Br.

Pyrolysis of V to VI.—A magnetically stirred mixture of V (10 g) with 4.5 g of potassium thiophenolate in 140 ml of redistilled *n*-heptyl alcohol was heated (under N_2) at 175–180° for 30 min. After cooling (under N_2) the system was diluted with 350 ml of Et_2O and extracted with twelve 40-ml portions of 0.4 *N* HCl. The combined acid extracts were washed several times with Et_2O (to remove residual heptanol) then cooled to 5°, basified with a slight excess of concentrated NH_4OH, and shaken with Et_2O. At this point a portion of the moderately soluble, crystalline VI separated and was removed by filtration (2.3 g). The dried ethereal extracts yielded a second crop (2.6 g). Recrystallization of the combined material from Et_2O yielded 3.45 g (46%) of pure VI, mp 180–181.5°, unchanged after an additional crystallization. The substance sublimes *unchanged* at 165–170° (0.05 mm); diazocryptophenol test was *negative*, $[\alpha]^{22}D$ −119.2 ± 1.0° (*c* 1.05), *m/e* 299. *Anal.* ($C_{18}H_{21}NO_3$) C, H, N, OCH_3.

The **oxime** was prepared by heating a mixture of 0.1 g of VI, 0.03 g of $NH_2OH \cdot HCl$, and 0.036 g of anhydrous NaOAc in 15 ml of 90% EtOH for 9 hr. Concentration to a small volume (*in vacuo*) and dilution with H_2O gave a colorless solid which was collected, dried, and recrystallized twice from MeOH; colorless prisms, mp 211–213°. *Anal.* ($C_{18}H_{22}N_2O_3$) C, H, N.

Further concentration of the mother liquors resulting from the crystallization of VI yielded a small quantity of slender prisms which, after a second crystallization from Et_2O, amounted to 0.68 g, mp 146–148°. The diazocryptophenol test was *positive* (*cf.* ref 14); $[\alpha]^{20}D$ +87.5 ± 1.0° (*c* 1.15); strong carbonyl peak at 5.85 μ. *Anal.* ($C_{18}H_{23}NO_3$) C, H.

Demethylation of VI to VII Hydrobromide.—A solution of VI (0.6 g) in 4.8 ml of 48% HBr was maintained at 160° (preheated oil bath) for 20 min during which interval a pale pink precipitate separated. After cooling and dilution with 15 ml of ice–H_2O, the product was collected and air dried, 0.7 g. Recrystallization from MeOH–Et_2O gave 0.6 g of light pink crystals, a sample of which was again recrystallized for analysis; mp 263–264° dec, $[\alpha]^{24}D$ −50.9 ± 2.0° (*c* 0.55), λ_{max}^{Nujol} 3.16 μ (hydroxyl). The diazotized sulfanilic acid–cryptophenol test was *negative*. *Anal.* ($C_{17}H_{20}BrNO_3$) C, **H**, Br.

Free Phenolic Base VII.—The above hydrobromide (0.5 g) was triturated with 8 ml of ice-cold 2 *N* NH_4OH, and the resulting colorless solid was collected, washed with H_2O, and air dried; after two recrystallizations from absolute EtOH, mp 217–219°, $[\alpha]^{24}D$ −122.7 ± 1.0° (*c* 1.19). The cryptophenol test was *negative*. *Anal.* ($C_{17}H_{19}NO_3$) C, H.

Reduction of VI to X. A. *Via* **$NaBH_4$.**—A magnetically stirred suspension of VI (0.75 g, 0.0025 mole) in 25 ml of MeOH was treated with a solution of 0.5 g (0.0125 mole) of $NaBH_4$ in 5 ml of MeOH and the system was stirred for 5 hr. After the addition of 15 ml of H_2O the clear solution was heated (steam bath) for 1 hr. Removal of the solvent at 40° (*vacuo*) yielded a pale pink gum which crystallized to a tacky solid when triturated with a little Et_2O, yield 0.6 g. Recrystallization from Et_2O gave 0.35 g of small, colorless prisms, mp 155–157°. It gave a *positive* cryptophenol test with diazotized sulfanilic acid, $[\alpha]^{20}D$ +72.3 ± 1.0° (*c* 1.36). *Anal.* ($C_{17}H_{25}NO_3$) C, H. Twin ir hydroxyl peaks at 2.75 and 2.85 μ were observed; carbonyl absorption, nil.

An additional 0.085 g of X was recovered from the partially concentrated mother liquor. Further concentration (*in vacuo*) of the second mother liquor afforded 0.15 g of pale yellow gum which gave a positive cryptophenol test and whose ir spectrum showed both hydroxyl and carbonyl peaks, indicative of incompletely reduced VI. **X·hydrobromide** was prepared by adding a slight excess of ethereal HBr to an Me_2CO solution of X and recrystallizing the salt from absolute EtOH; mp 287–289° dec.

Anal. ($C_{18}H_{26}BrNO_3$) C, H, Br.

B. *Via* **PtO_2.**—A solution of VI (0.75 g) in 65 ml of MeOH was shaken in H_2 with 0.15 g of PtO_2 for 50 hr (H_2 uptake 1.95 moles). Concentration of the filtered solution (*in vacuo*) gave a foam which was dissolved in 6 ml of Me_2CO and treated with ethereal HBr. The resulting crystalline solid (0.8 g) was recrystallized from absolute EtOH and yielded 0.5 g of small prism clusters, mp 280–282° dec, whose ir spectrum (Nujol) was identical with that of the hydrobromide of the $NaBH_4$ reduction product (above). Regeneration of the free base (NH_4OH–Et_2O) and two recrystallizations from Et_2O gave colorless prisms, mp 154–156° (cryptophenol test *positive;* ir spectrum identical with that of $NaBH_4$ reduction product above).

Reduction of V to VIII. A. *Via* **$NaBH_4$.**—To a suspension of V (0.5 g) in 20 ml of methanol, 0.3 g of $NaBH_4$ in 2.5 ml of methanol was added, and the system was stirred for 6 hr. The clear solution was diluted with 5 ml of distilled H_2O and, after 30 min, concentrated (*in vacuo*, 35°) to a colorless solid which was triturated with a few drops of MeOH, collected, and dried (0.27 g); after two crystallizations from MeOH–Et_2O, mp 233–235° dec, the diazocryptophenol test was *negative*, $[\alpha]^{21}D$ +44.6 ± 1.0° (*c* 1.09). *Anal.* ($C_{19}H_{26}BrNO_3$) C, H.

B. *Via* **PtO_2.**—One mole of H_2 was absorbed when a solution of V (1.5 g) in 150 ml of MeOH was shaken in H_2 with 0.2 g of PtO_2 (6 hr). Concentration of the filtered solution (*in vacuo*, 40°) gave 1.45 g of a colorless solid, a sample of which was twice recrystallized from MeOH–Et_2O; mp 238–239° dec. The diazocryptophenol test was *negative;* $[\alpha]^{22}D$ +42.0 ± 1.0° (*c* 1.08). *Anal.* ($C_{19}H_{26}BrNO_3$) C, H.

Pyrolysis of VIII to IX.—A stirred suspension of VIII (3 g) in 45 ml of *n*-heptyl alcohol was heated (under N_2) at 185–195° for *ca.* 40 min. After cooling, the system was diluted with 450 ml of Et_2O and filtered from some unreacted VIII (0.4 g). Further traces of VIII were removed by washing the filtrate three times with H_2O after which the basic material was extracted with six 35-ml portions of 0.3 *N* HCl. Liberation of the product (NH_4OH–Et_2O) yielded 1.6 g of a colorless solid which was fractionally crystallized (MeOH) into two components, IX (0.69 g), mp 163–165°, and IXa (0.36 g), mp 148–150° (mmp 130–136°). The former separates as thick, six-sided plates while the latter appears as slender, prismatic rods; **IX**: *Anal.* ($C_{19}H_{23}NO_3$) C, H. $[\alpha]^{27}D$ +126.6 ± 0.8° (*c* 1.26), strong ir carbonyl peak at 5.85 μ. The **oxime**, prepared in the usual manner, was amorphous. *Anal.* ($C_{18}H_{24}N_2O_3$) N. The **perchlorate**, prepared in Me_2CO with a slight excess of an Me_2CO solution of $HClO_4$, was recrystallized twice from *i*-PrOH; mp 188–191°. *Anal.* ($C_{18}H_{24}ClNO_7$) C, H.

IXa: *Anal.* ($C_{18}H_{23}NO_3$) C, H. $[\alpha]^{22}D$ +87.6 ± 1.0° (*c* 1.03), strong ir carbonyl peak at 5.85 μ (*cf.* ref 14).

$NaBH_4$ Reduction of IX to X.—A solution of IX (0.25 g) in 13 ml of MeOH was treated with 0.17 g of $NaBH_4$ (in 3 ml of MeOH) and the system stirred for 5 hr. After adding 5 ml of distilled H_2O, the clear solution was heated (steam) for 1 hr, then concentrated (*in vacuo*, 45°) to a gum which crystallized when triturated with a little Et_2O. Following a single passage through 0.2 *N* HCl and recovery (NH_4OH–Et_2O), the cryptophenolic base was crystallized from Et_2O; 0.15 g. A specimen was recrystallized again; mp 150–152°. The infrared spectrum of this substance was identical with that of X (derived from VI either by $NaBH_4$ or PtO_2 reduction); $[\alpha]^{20}D$ +70.0 ± 1.0° (*c* 0.979).